

III. Remarks

A. Amendments to the Claims

Claims 8–9, 13–16 and 20–25 have been amended to recite that the colloid is modifying the particles.

Support for the amendment is provided in the Specification at page 7, lines 1–5.

B. Rejection Under 35 U.S.C. Section 103 – Obviousness

Claims 8, 9, 13–16 and 20–25 are rejected under 35 U.S.C. Section 103(a) as being unpatentable over United States Patent No. 6,919,070 to Rudin et al., in view of United States Patent No. 5,560,932 to Bagchi et al.

1. The Examiner's reasons for the rejection

The Examiner's reasons for the rejection are set forth in the Action under the headings "Applicant's Arguments" and "Examiner's Response." For convenient reference these reasons are reproduced below:

Applicant's Arguments

Applicant argues the hydroxyapatite disclosed by Rudin et al. is pure hydroxyapatite crystals whereas the components of the instant invention have a water-soluble protective coating. Therefore the reference does not disclose Applicant's claimed suspension. The process of making the particles is different from the process used to make the particles of Bagchi et al. The process of the instant claims results in colloids forming intermolecular cross-linkages. The particles of Bagchi et al. are essentially free of intermolecular cross-linkages.

Examiner's Response

Applicant appears to be arguing the references separately and not as combined teachings. Although the hydroxyapatite of Rudin are pure hydroxyapatite, the teachings of Bagchi et al. would motivate one of ordinary skill in the art to coat the hydroxyapatite to inhibit aggregation due to inter-particle attractive forces. Further the types of cross-links are not recited in the instant claims. The claims recite the colloids are absorbed on the particles and make no mention of cross-links. "Absorbed" also encompasses "coat." As previously asserted in the previous office action in regard to the method of making the colloidal system, the instant disclosure teaches several ways to make the colloidal systems of the instant claims (see page 7 of the instant specification). It appears not all of the methods of making the product of the instant claims required an initial acidic solution in order to make the compositions of the instant claims. Further, the product of the instant claims and the product of the combined reference have the same function as being used in an oral composition and restoring dental enamel. The prior art product appears to differ from the claim product only in the method of obtaining the product. ***The burden of persuasion is on Applicant to show that the claimed product exhibits unexpected properties compared with that of the prior art.*** See MPEP 2144.04. ***Although Applicant asserts a material with different properties is yielded from the procedures of the instant claims than what is taught in the combination of references, there appears to be no evidence to support that the compositions have different properties provided in the instant disclosure or the filed Declarations.*** Note that the burden is higher for applicant due to the "peculiar nature" of product by process claims, as discussed therein. (*Emphasis added*).

(Examiner's Action at page 2, line 14, to page 4, line 4).

**2. Legal standard for determining whether
Applicants' claims are obvious under 35 U.S.C. Section 103**

The legal interpretation of Section 103 to be applied is set forth in the recent Supreme Court decision of *KSR International Co. v. Teleflex Inc. (KSR)*, 550 U.S. __, 82 USPQ2d 1385 (2007). *KSR* cites *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 148 USPQ 459 (1966) as setting out an objective analysis for applying Section 103. (82 USPQ2d at 1388). The objective analysis is as follows:

Under § 103, the scope and content of the prior art are to be determined; the differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, *etc.*, might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

(148 USPQ at 467).

Accordingly, the factual inquiries set forth by the Court are as follows:

- [T]he scope and content of the prior art are . . . determined;
- Differences between the prior art and the claims at issue are . . . ascertained;
- The level of ordinary skill in the prior art [is] resolved; and
- Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, *etc.*, might be utilized. . . .

3. The Application of the *Graham v. John Deere Co.*, factual standards

The application of the *Graham v. John Deere Co.* factual standards is being made with Declarations of Dr. Christian Kropf, one of the inventors of the invention disclosed and claimed in this application.

The Third Declaration of Christian Kropf was originally filed with Applicants' Amendment and Response dated February 4, 2008, and attached thereto as **EXHIBIT B**.

For the filing of Applicants' present Amendment and Response, the Third Declaration of Christian Kropf is attached and designated **EXHIBIT A**. The Fourth Declaration of Christian Kropf is attached and designated **EXHIBIT B**. The Fifth Declaration of Christian Kropf is being filed concurrently with Applicants' Response and designated **EXHIBIT C**.

(a) Determining the scope and content of the prior art

The Rudin et al. patent discloses a composition characterized in that it comprises particles of hydroxyapatite with an average particle size in length (l), width (d), and thickness (h). The values for these dimensions are: (l) from 0.2 μm to 0.01 μm , (d) 0.1 μm to about 0.001 μm and (h) from 0.1 μm to 0.0001 μm (column 2, lines 22-27) (Third Declaration of Christian Kropf, Paragraph 5).

Rudin et al. further discloses that the hydroxyapatite being introduced into the composition possesses osteo-reparative properties and contains preferably about 100% $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ and that the specific surface of hydroxyapatite used in the composite advantageously is 100 to 150 m^2/g (column 2, lines 41-45). This disclosure indicates that the hydroxyapatite disclosed in Rudin et al. is pure hydroxyapatite (Third Declaration of Christian Kropf, Paragraph 6).

Rudin et al. further discloses an oral product that will comprise a liquid phase containing humectants and binding thickeners which act to maintain the particulate solid abrasive and hydroxyapatite crystals in the form of stable suspension in liquid phase (column 3, lines 11-15). On the basis of the disclosure in Rudin et al., the hydroxyapatite crystals in the suspension are pure hydroxyapatite (Third Declaration of Christian Kropf, Paragraphs 6 and 7).

The conclusion that the hydroxyapatite particles disclosed in Rudin et al. are pure is further based on the disclosure at column 2, lines 46-51 of Rudin et al. that U.S. Patent No. 6,254,855 B1 describes a method for producing a suspension of hydroxyapatite as described in the Rudin et al. application. U.S. Patent No. 6,254,855 B1 discloses in EXAMPLE 1 that according to the method described in that patent, a pure stoichiometric hydroxylapatite in a suspension form is produced free of admixtures (column 3, lines 43-67) (Third Declaration of Christian Kropf, Paragraph 8).

The Bagchi et al. patent describes the preparation of a nanoparticulate dispersion and the resulting nanoparticles. The process is summarized in the Abstract, the pertinent portion of which is set forth below.

This invention describes the preparation of nanoparticulate pharmaceutical agent dispersion via a process that comprises the dissolution of the said pharmaceutical agent in an alkaline solution and then neutralizing the said solution with an acid in the presence of a suitable surface-modifying, surface-active agent to form a fine particle dispersion of the said pharmaceutical agent.

(Fourth Declaration of Christian Kropf, Paragraph 5).

Bagchi et al. discloses the objective of the invention at column 3, lines 7-16, which is quoted herebelow:

It would be desirable to provide stable dispersible drug or pharmaceutical agent particles in submicron size range which can be readily prepared which do not appreciably flocculate or agglomerate due to interparticle attraction forces, and do not require the presence of a crosslinked matrix, simultaneously providing enhanced bioavailability of the drug. Furthermore, it would be highly desirable that such formulations do not involve removal of toxic residues such as toxic solvents or heavy metal solubilizates that arise out of attrition of the milling media.

(Fourth Declaration of Christian Kropf, Paragraph 6).

The accomplishment of this objective by the Bagchi et al. invention is referred to in the following description of the advantages of the invention.

It is an advantageous feature that a wide variety of surface modified drug nanoparticles free of unacceptable contamination can be prepared in accordance with this invention. (Column 3, lines 50-52).

A further advantage of the method is that unlike solvent precipitation, the final product of this invention is free of any trace of trace solvents that may be toxic and must be removed by expensive treatments prior to final product formulation. (Column 4, lines 7-11).

(Fourth Declaration of Christian Kropf, Paragraph 7).

Bagchi et al. further discloses that the surface modifier physically adheres to the surface of the pure pharmaceutical agent particles but does not chemically bond. This disclosure in Bagchi et al. is set forth below for convenient reference

The particles of this invention contain a discrete phase of a said substance as described above having a surface modifier adsorbed on the surface thereof. Useful surface modifiers are believed to include those which physically adhere to the surface of the drug substance but do not chemically bond to the drug.

The particles of the invention, the process of making the particles and a preferred utility are disclosed in the paragraph directly under the heading “Description of Preferred Embodiments.” That paragraph is set forth below.

This invention is based partly on the discovery that pharmaceutical agent particles having an extremely small effective average particle size can be prepared by homogeneous nucleation and precipitation in the presence of a surface modifier, and that such particles are stable and do not appreciably flocculate or aggregate due to interparticle attractive force and can be formulated into pharmaceutical compositions exhibiting unexpectedly high bioavailability. (Column 4, lines 40-48).

(Fourth Declaration of Christian Kropf, Paragraph 8).

Bagchi et al. discloses that the particles comprise a pharmaceutical agent substance in a discrete crystalline phase. (Column 4, lines 56-61) (Fourth Declaration of Christian Kropf, Paragraph 9).

Bagchi et al. discloses that the surface modifier adheres to the surface of the particles but is essentially free of intermolecular linkages between the molecules of the modifier, and between the modifier and the particles, due to the lack of chemical bonds between the surface modifier and [drug] particle. This disclosure in Bagchi et al. is set forth in the passage herebelow.

The surface modifier is adsorbed on the surface of the pharmaceutical agent in an amount sufficient to maintain an effective average particle size of less than about 400 nm. The surface modifier does not chemically react with the drug substance or itself. Furthermore, the individually adsorbed molecules of the surface modifier are essentially free of intermolecular crosslinkages. (Column 6, lines 20-26).

(Fourth Declaration of Christian Kropf, Paragraph 10).

**(b) Ascertaining the differences
between the prior art and the claims at issue**

Accordingly, a combination of the disclosures of Rudin et al. and Bagchi et al. results in the production of pure nanoparticles of a pharmaceutical agent substance including hydroxyapatite. In the Bagchi et al. disclosure the particles in the form of a discrete crystalline phase have a surface modifier adsorbed onto the particles. The surface modifiers may physically adhere to the surface of the drug substance but do not chemically bond to the drug.

Claim 8 of the application is directed to a suspension. The remaining claims 9, 13–16 and 20–25 are directed to a toothpaste comprising the suspension, or other suspensions within the scope of claim 8. Claim 8 reads as follows:

Claim 8. A suspension of one or more phosphate calcium salts, or fluorophosphate calcium salts in a liquid medium in which the salts are less than 1 g/l soluble, wherein the calcium salts comprise primary particles having diameters of from 5 to 50 nanometers and lengths of from 10 to 150 nanometers, wherein the calcium salts are formed by precipitation reactions from acidic aqueous solutions of water-soluble calcium salts and aqueous solutions of water-soluble phosphate salts at an increased pH using an aqueous alkali or ammonia and in the presence of a content of at least 0.01% by weight, based on the weight of the suspension, of a water-soluble polymeric protective colloid selected from the group consisting of gelatin, casein, starch, plant gums, cellulose ethers, methylcellulose, hydroxyethylcellulose, carboxymethylcellulose, hydroxyethylstarch and hydroxypropylguar, resulting in the colloid being adsorbed onto and modifying said particles and the particles being stabilized against agglomeration.

Applicants' precipitation reactions occur under conditions of increasing pH using an aqueous alkali or ammonia in the presence of one or more of Applicants' claimed colloids rather than under conditions of decreasing pH as disclosed in Bagchi et al. Applicants' precipitation reactions of acidic aqueous solutions of water-soluble calcium and phosphate or fluoride salts, in the presence of a colloid, and at an increasing pH, results in particles having a more intense structure in which, in Applicants' claimed particles, the colloid forms intermolecular crosslinkages with the particles. In contrast, in the Bagchi et al. particles, the surface modifiers (*i.e.*, colloid) are essentially free of intermolecular crosslinkages. (Fourth Declaration of Kropf, Paragraph 12).

This more intense structure is further defined in the amendment to the claims that the colloid ***is modifying*** said particles (*emphasis added*).

In support of Applicants' position that Applicants' claimed particles and colloid are crosslinked, Applicants submit as **EXHIBIT C** the Fifth Declaration of Christian Kropf. Dr. Kropf's Declaration is based on data submitted in United States Patent Application No. 11/864,252, for which he is the first-named inventor. (Fifth Declaration of Christian Kropf, Paragraph 3).

United States Patent Application No. 11/864,252 includes a TEM micrograph of a composite according to the invention, comprising hydroxylapatite and Type A gelatine. (A copy of the TEM micrograph is attached to the Fifth Declaration of Christian Kropf as **EXHIBIT 1**). According to Paragraph [0021] of Kropf application '252, "[T]he three-dimensional structure of the composite materials according to the invention of a protein component and the poorly soluble nanoparticulate calcium salt is illustrated by way of example by the TEM micrograph in Fig. 1 of a composite material of hydroxylapatite and Type A gelatine (magnification 200,000 x; 1 cm. in Fig. 1 corresponds to 40 nm)." (Fifth Declaration of Christian Kropf, Paragraph 4).

Processes according to the invention are generally described in Paragraphs [0044] – [0048] of Kropf application '252. Paragraph [0044] describes the process as follows:

The composite materials according to the invention are prepared by precipitation reactions from aqueous solutions of water-soluble calcium salts and aqueous solutions of water-soluble phosphate and/or fluoride salts, the precipitation being carried out in the presence of protein components. This is preferably done by adding the protein components in pure, dissolved or colloidal form to the alkaline aqueous phosphate and/or fluoride salt solution or to the alkaline solution of the calcium salt before the precipitation reaction. Alternatively, the protein components may be initially introduced in pure, dissolved or colloidal form followed by addition of the alkaline calcium salt solution and the alkaline phosphate and/or fluoride salt solution either successively in any order or at the same time.

(Fifth Declaration of Christian Kropf, Paragraph 5).

The process disclosed in Paragraph [0044] of Kropf application '252, comes within the process set forth in all of Applicants' claims. Paragraphs [0045] – [0048] disclose variants of the process disclosed in Paragraph [0044] that also come within the process claimed in all of Applicants' claims. *See also* Paragraph [0027], which discloses that "gelatin is preferred [protein] for the purposes of invention" and Example 2.1 (Paragraph [0071]), which employs as the protein, gelatin. (Fifth Declaration of Christian Kropf, Paragraph 6).

Paragraph [0021] of Kropf application '252 also discloses that "[T]he way in which the inorganic particles are attached to the basic skeleton of the protein component (*i.e.*, the gelatin) is determined by the primary structure (amino acid sequence) and — depending on the nature of the protein component — by its secondary, tertiary and quaternary structure. It has surprisingly been found that the spatial distribution and the quantitative extent of the attachment of the inorganic nanoparticles to the protein component can be influenced by the type and quantity of the amino acids present in the protein component, and hence by the choice of the protein components." (Fifth Declaration of Christian Kropf, Paragraph 7).

In summary, Applicants' claimed suspension the claimed particles comprise the inorganic nanoparticles attached to the basic skeleton of the gelatin, *i.e.*, the colloid, to form a single entity that is linked together. Applicants' claimed colloid is both adsorbed onto and modifies the particles as now set forth in the claims. In contrast to Applicants' claimed particles which are "attached to," *i.e.*, bonded to the colloid, the Bagchi et al. particles and colloid must be essentially free of chemical links. (Fifth Declaration of Christian Kropf, Paragraph 8).

Applicants' claimed particles, which are attached to the colloid, form a single structure, whereas the particles disclosed in Bagchi et al. do not because the particles and surface modifier are free of chemical links. (Fifth Declaration of Christian Kropf, Paragraph 9).

Applicants' claimed inorganic nanoparticles reproduce the three-dimensional structure of the gelatin, *i.e.*, the colloid. Hence, Applicants' claimed product is different in both composition and structure from the Bagchi et al. product. (Fifth Declaration of Christian Kropf, Paragraph 10).

The structured composite materials produced according to Applicants' claimed process lead to a particularly effective biomineralization process. (Fifth Declaration of Christian Kropf, Paragraph 11).

The structure of the composite materials and the charging of the protein component with the nanoparticulate calcium salt can be influenced by surface modification. In this way, where the composite materials are used in remineralization processes, it is possible to influence both the course and the speed of the remineralization process. (Fifth Declaration of Christian Kropf, Paragraph 12).

(c) Resolving level of ordinary skill in pertinent art

The inventors of the present application, one of whom is Dr. Christian Kropf, and the inventors of the Rudin et al. and Bagchi et al. patents, would represent persons of ordinary skill in the art.

(d) Possible utilization of secondary considerations

As set forth in *Graham v. John Deere Co.*:

Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, *etc.*, might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

(148 USPQ at 467).

As set forth above, Rudin et al. and Bagchi et al. have failed to discover, let alone exemplify, disclose or suggest to one of ordinary skill in the art, Applicants' claimed suspension.

4. Applicants' response to Examiner's reasons for rejections of claims

On page 3, lines 4-17, the Examiner has listed a number of reasons in support of the rejection of the claims. Applicants' have addressed herebelow these reasons separately, starting with the issue of differences in properties between Applicants' claimed particles and the particles that would be obtained by following the combined disclosures of Rudin et al. and Bagchi et al.

(a) Claimed product exhibits different and unexpected properties

The Examiner has asserted that the burden of persuasion is on Applicants to show that the claimed product demonstrates unexpected properties compared with the prior art.

As noted above, the composition and structure of Applicants' claimed particles are different than the particles obtained from the combined disclosures of Rudin et al. and Bagchi et al. The particles obtained from the combined disclosures of Rudin et al. and Bagchi et al. have by design essentially no chemical links between the pure pharmaceutical particles and the surface modifier which instead physically adheres to the pure particles. That is because Rudin et al. and Bagchi et al. are directed to the formation of pharmaceutical particles that are pure, *i.e.*, contain no impurities.

In contrast, Applicants' claimed suspension comprises particles in which the primary nanoparticles are attached to the colloid to a degree that the particles take on the structure of the colloid. Obviously, these differences in composition and structure result in differences in properties. Indeed, Applicants' particles, which take on the structure of the colloid, have improved biomedical properties.

As noted above, surface modification can influence the structure of the composite materials and the charging of the protein component with the nanoparticulate calcium salt. This surface modification of Applicants' claimed particles further distinguishes the particles from the particles that would be derived from the combined disclosures of Rudin et al. and Bagchi et al.

**(b) Examiner's contention that Applicants argue
the references separately**

Under the factual inquiries of *Graham v. John Deere*, the scope and content of the prior art are "... determined." Applicants have determined the scope and content of each of Rudin et al. and Bagchi et al. individually and in combination.

(c) Examiner's contention that type of crosslinks formed is not recited in instant claims

The Examiner has conceded that Applicants claim a different process than the process disclosed in the combination of Rudin et al. and Bagchi et al. Applicants have demonstrated that Applicants' claimed particles differ from the particles obtained by the combined disclosures of Rudin et al. and Bagchi et al. in terms of composition, structure and properties. Therefore, as Applicants' claims are different from the combined disclosures in Rudin et al. and Bagchi et al. in terms of process and in the composition structure and properties of the particles, there is no need for Applicants to set forth in the claims the type of crosslink in order to make the claims patentable over the combination of Rudin et al. and Bagchi et al.

(d) Examiner's contention that claims recite that colloids are adsorbed onto particles and make no mention of crosslinks

As noted above, Applicants' claimed suspension is distinct from the combined disclosures of Rudin et al. and Bagchi et al. by reason of differences in Applicants' claimed process and the composition, structure and properties of Applicants' claimed particles. Accordingly, the claims do not require mention of crosslinking.

(e) Term "adsorb" also comprises "coat"

As Applicants' bases for patentability of the claimed suspension over the combined disclosures of Rudin et al. and Bagchi et al. are not based on the term "adsorbed," this reason for the rejection of the claims has now been rendered moot.

(f) Instant disclosure teaches several ways to make colloidal system of the claims are limited to a Markush group of preferred colloids

Applicants' claimed suspension defines colloids in terms of a Markush group of compounds selected from the compounds recited in the Specification at page 7, lines 5-12.

(g) Not all methods require initial acidic solution

Applicants' claims are directed to a preferred method of preparing Applicants' claimed suspension and Applicants' claimed primary particles.

5. Applicants' claimed suspension is not obvious under 35 U.S.C. Section 103

Accordingly, for the reasons set forth above, the rejection of claims 8–9, 13–16 and 20–25 under 35 U.S.C. Section 103(a) as being unpatentable over United States Patent No. 6,919,070 to Rudin et al. in view of United States Patent No. 5,560,932 to Bagchi et al. is untenable and should be withdrawn.

IV. Conclusion

It is believed that the above Amendment and Remarks constitute a complete response under 37 C.F.R. Section 1.111 and that all bases of rejection in the Examiner's Action have been adequately rebutted or overcome. A Notice of Allowance in the next Office Action is, therefore, respectfully requested. The Examiner is requested to telephone the undersigned attorney if any matter that can be expected to be resolved in a telephone interview is believed to impede the allowance of pending claims 8-9, 13-16 and 20-25 of United States Patent Application Serial No. 09/868,379.

Respectfully submitted,

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